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(54) **Pharmaceutical formulations containing a mixture of higher primary aliphatic alcohols in the treatment ofhypercholesterolaemia and hyperlypoproteinaemia type II and stimulation of sexual behavior in animals and humans.**

(57) The present invention relates to the pharmaceutical industry and, in particular, to formulations presenting hypercholesterolaemic activity and reduction of LDL levels (Low Density Lipoproteins), as well as important properties for the enhancement of sexual capacity in animals.
The main objective of this invention is to elaborate different pharmaceutical formulations for its oral and parenteral administration, aimed at lowering blood cholesterol, triglycerides and low density lipoproteins. As an active compound, these formulations contain a mixture of saturated primary alcohols having a straight chain ranging from 24 to 34 carbon atoms in specific relation to each other.

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The present invention is mainly related to the pharmaceutical industry and, in particular, to the effective formulation of hypercholesterolaemia and reduction of LDL levels. It has also proven to be an important stimulator of sexual behavior. As an active compounds, these formulations contain a mixture of saturated primary alcohols having a straight chain ranging from 24 to 34 carbon atoms in specific relation to each other.

The first objective of this invention is to use a mixture of higher primary aliphatic alcohols obtained from sugar cane wax as an active compound.

The second objective is the formulation of pharmaceutical components whose active compound is the mixture of higher primary aliphatic alcohols with important pharmacological properties to be administered both orally and parenterally.

A third objective is to apply such formulations to the treatment of hypercholesterolaemia, hyperlypoproteinaemia type II and sexual disorders.

And finally the management of these pathologies by means of a therapeutically adequate dosage of this active compound.

Drugs with specific pharmacological properties based on the use of a mixture of higher primary fatty alcohols as an active compound are not known.

Formulations used as nutritional supplementation based on mixtures of higher primary fatty alcohols have been obtained in recent years, especially in an attempt to find the ergogenic properties reported first in the case of wheat germ oil and later in octacosanol.

In 1985, Sanyu Shoji (JP 85-49775) reported the components of a dietary supplementation containing *Eleutherococus senticosus* extract, pangamic acid and octacosanol, the latter accounting for 30 to 60 % of the dietary supplementation which increases the general activity of internal organs such as the heart, the liver and the kidneys. The Japanese patent JP 85- 119514 is associated with the obtention of higher primary aliphatic alcohols from sugar cane wax. It also reports that octacosanol has two main effects, namely, to increase physical strength and to restore the damaged nervous cells as well as to lower blood pressure and improve muscular functions including the myocardium.

Patent JP 87-224258 includes the formulation of a nutritional food based on the addition of different types of lipids such as palmitic acid, docohexanoic acid, eicosapentanoic acid, linolenic acid, lecithins, vitamin E and octacosanol as dietary supplementation. This dietary supplementation was administered to rats which were previously fed with a high cholesterol diet. The accumulation of blood cholesterol was eliminated after two weeks'treatment. The hypocholesterolaemic properties of this product derive mainly from the presence of fatty acids and lecithins.

Nogushi *et al*, patent JP 88-116645, report the formulation of a candy containing octacosanol used as an ergogenic supplementation at a 1:89 ratio in diets of rats subject to physical activity. This physical activity lasted two weeks and, afterwards, it was found that glycogen levels in muscles and liver had decreased in relation to normal-diet animals.

According to patent JP 79-10539, another property reported in the case of octacosanol is that of increasing the presence of sex hormones. Similarly, it states that octacosanol regulates hormonal functions.

Many commercial products with ergogenic properties based on mixtures of higher primary alcohols are also known, as for example the so-called Endurol which contains 33 % octacosanol, 35 % triacontanol, 20 % tetracosanol and 12 % hexacosanol. The Viobin company has marketed an ergogenic tonic based on the same higher primary alcohols, though in different amounts. It has been reported that this tonic contains 33 % octacosanol, 41.6 % triacontanol, 16.6 % tetracosanol and 8.3 % hexacosanol.

In Japanese patents JP 85-49775 and JP 87-224258 reference is made to 26-30 carbon atoms saturated alcohols generally presenting the same physiological properties. However, previous studies have shown that this is not so. For example, Jones *et al* (1979), in experiments carried out with Chalydomonas, proved that TRIA stimulates growth and assimilation of $CO_2$ by photosynthesis while octacosanol inhibits TRIA effects during the $CO_2$ assimilation process. In similar studies, Ries *et al* ( 1987) found that octacosanol inhibits triacontanol plant growth promotion properties. Subsequent in vitro experiments by Lesniak *et al* (1989) indicate that triacontanol increasingly stiinulates ATPase activity in Barley vesicle membrane (Hordeum vulgare) while octacosanol did not.

There is also another study (Borg *et al*, 1987) regarding the effect of long chain alcohols in neural growtch which reveals that hexacosanol is a powerful neural growth stimulator. Alcohols of 16, 20, 22, 24, 28 and 30 carbon atoms had no significant effects.

Hiroko Sho *et al*, ( 1984) studied the effects of Okinawa sugar cane wax on serum and liver lipid levels in rats subjected to diets containing 0.5 % of this sugar cane wax and found a significant reduction of cholesterol levels in these rats' serum and liver. No significant variations in cholesterol levels were found when using fatty alcohols from this wax in these diet-fed rats. Shumiko Shumira *et al*, (1987) studied the octacosanol effects in mice subject to physical activity and fed with octacosanol enriched diets. These assays showed that

octacosanol increases physical strength. At the same time, they found a significant decrease of neutral lipids and cholesterol levels in the liver without modifications in the phospholipids content. Nevertheless, reduction of serum cholesterol and lipoprotein levels were not observed. There are different commercial drugs used in the treatment of hypercholesterolaemic patients which lower cholesterol levels by 30 % but they all provoke a number of negative effects. For example, Lopid used in the treatment of hypercholesterolaemia, reduces LDL-cholesterol by 5.4 and 6.9 % but it decreases sexual capacity in some patients, causes skin rash, headaches and blurred vision. Likewise, it should not be administered to patients with renal failure. Probucol, which causes a 10 % mean decrease of cholesterol level and from 10 to 15% LDL-cholesterol, produces gastrointestinal disturbances, nauseas, abdominal pain, diarrheas and flatulence in 10 % of the population, as well as a considerable variation in the electrocardiogram.

Another product used in the treatment of hypercholesterolaemic patients is Cholestyramine. This drug is highly efficient as hypocholesterolaemic since it lowers serum cholesterol levels by 39 % and LDL by 30 %. However, this product has some disadvantages since the dosage required is relatively high (16-20 g daily), causing constipation and interacting with other drugs like Digitoxin.

Mevacor has been broadly used in recent years due to its rapid and lowering effects in cholesterol levels, namely 32 % reduction of cholesterol and 39 % of LDL. The disadvantage of this product is that it provokes a number of adverse effects including gastrointestinal disturbances, headaches, subcutaneous rash, pruritus, and severe muscular lesions in sensitive patients resulting in myolisis, and testicular atrophy. It increases creatinekinase and transaminase since hepatic tumors in laboratory animals have been reported. Zocor is a Mevacor by-product causing mild adverse effects. Reportedly, constipation, flatulence, nausea, headache, fatigue, subcutaneous rash and myopathies affecting creatinekinase are some of the disadvantages of this product. One of the objectives of this invention is to use the mixture of saturated primary fatty alcohols with 24 to 32 carbon atoms as a component of the pharmaceutical formulation. The mixture formulation has been determined by using gas chromatography in a capillary column, the formulation of the mixture is derivatized when these alcohols are dissolved in pyridine and are silonized using N-methyl-N-TMS-trifluoracetamide (MSTFA). Table I shows the qualitative and quantitative results of the mixture.

**TABLE I**

**Qualitative and quantitative formulation of the mixture of primary fatty alcohols used**

| Component | Proportion in the mixture (%) |
|---|---|
| tetracosanol | 0.5 - 5.0 |
| hexacosanol | 5.0 - 15.0 |
| heptacosanol | 0.5 - 5.0 |
| octacosanol | 55.0 - 80.0 |
| nonacosanol | 0.5 - 3.0 |
| triacontanol | 6.0 - 20.0 |
| dotriacontanol | 1.0 - 10.0 |
| tetratriacontanol | 0.0 - 2.5 |

The aim of this invention is that the mixture of saturated primary alcohols provoked an active compound in pharmaceutical formulations is made up by saturated primary alcohols having a long chain ranging from 24-34 carbon atoms. This alcohol mixture is obtained from sugar cane wax, a semi-crystalline, off-white color solid with a 78.0 - 82.5 °C fusion temperature.

This mixture is obtained from different types of waxes through a homogeneous stage saponification process and its subsequent extraction with organic solvents.

The remarkable aspect of this finding is that the mixture of alcohols causes a marked reduction of cholesterol and other low density serum lipoproteins (L DL) which is of great importance in the control of risk factors. The mean reduction of cholesterol and LDL in this experiment is 12 and 13 % respectively. Furthermore, in comparative studies on the effects of octacosanol and the mixture of alcohols in blood lipid levels, we have found that the alcohol mixture -as an active compound- lowers serum cholesterol levels, changes plasmatic lipoproteins patterns, increases high density lipoproteins (HDL) and lowers LDL thus causing an increase in the HDL/LDL ratio while with the use of octacosanol this effect was not observed

The aforementioned findings are amazing if we take into account that Hiroko *et al* (1984) were not able to

obtain significant results on serum lipid levels with the use of fatty alcohols from the Okinawa sugar cane.

The daily dosage of the mixture of alcohols suitable for hypercholesterolaemia treatment is from 1 to 50 mg. The most adequate administration way is orally through coated tablets of granules although this drug can be administered parenterally.

The pharmaceutical formulation single dose to be orally administered contains, mostly as an active substance, from 0.5 to 5 wt% of the alcohol mixture. This dosage is obtained by mixing the active substance with different excipients in the pharmaceutical formulation either as agglutinants, disintegrators, lubricants, sliders or just fillers.

The drug proposed by this invention is relatively innocuous according to the results obtained in acute, subacute, subchronic and chronic toxicity assays carried out in rodents as well as in chronic studies in monkeys. They do not reveal any teratogenic activity in rats or rabbits, nor do they have a mutagenic potential.

No side-effects have been detected in patients treated with the drug resulting from this invention. However, when administered, there is an increase of sexual activity of laboratory animals, whose mechanism of action is only based on the increase of libido, this effect having no relation with the level of sexual hormone mainly involved in the control of such behavior. There is a number of patients who have also referred to this effect.

The objective of this invention will be further on detailed and will refer to the examples which will not be restricted to the scope of said invention.

**Example 1**

1 kg of raw sugar cane wax is taken to which a homogeneous phase saponification process is applied followed by the extraction of primary fatty alcohols using the adequate organic solvents. 105 g of said alcohols mixture were obtained. The fusion temperature of the alcohol mixture ranges from 78.0 to 82.0 °C and the purity of the mixture is 92.98 %.

**Example 2**

Out of 2.5 kg of refined sugar cane wax, following the method used in the aforementioned example, 438.6 g of alcohol mixture were obtained in this case accounting for a 95.91 % purity and the fusion temperature ranged from 79.5 to 82 °C.

For analysis of alcohols through gas chromatography in a capillary column of fused silica, these alcohols are derivatized by using N methyl-N-TMS-trifluoroacetamide (MSTFA) dissolved in pyridine. Table II shows the results of qualitative and quantitative analysis in both examples.

**TABLE II**

**Qualitative and quantitative composition of the mixture of higher aliphatic alcohols obtained**

| Identified component | Percentage of alcohols | |
|---|---|---|
| | In example 1 | In example 2 |
| tetracosanol | 2.08 | 2.81 |
| hexacosanol | 9.68 | 7.57 |
| heptacosanol | 3.16 | 2.81 |
| octacosanol | 68.30 | 73.99 |
| nonacosanol | 0.44 | 0.85 |
| triacontanol | 8.17 | 6.41 |
| dotriacontanol | 1.05 | 1.35 |
| tetratriacontanol | 0.10 | 0.12 |
| Total | 92.98 | 95.91 |

**Example 3**

From the mixture of higher alcohols obtained in Example 2, 5 mg tablets were made from the alcohol mixture containing the components listed in Table III.

**TABLE III**

**Pharmaceutical formulation of the 5 mg tablets**

| Component | % in tablet |
|---|---|
| Mixture of higher aliphatic alcohols | 4.5 |
| Lactose | 75.0 |
| Corn starch | 15.0 |
| Gelatin | 1.5 |
| Sodium croscarmelose | 1.0 |
| Talc | 2.0 |
| Magnesium estearate | 1.0 |

## Example 4

The tablet formulation containing 5 mg of the reported mixture of alcohols is administered to a group of 16 patients affected with hyperlypoproteinaemia type II (according to Frederickson's classification, 1967). Before these patients were included in the assay, they were subjected to a 4 weeks diet and only those who still had a high LDL were treated. The diet element was continued throughout the study and the research carried out on the main lipid-lowering drugs available. Treatment was continued for 8 weeks, whereby each patient was administered a daily tablet with the formulation described in the previous example. Laboratory assays were conducted after 4 and 8 weeks, and parameters in Tables IV and V were evaluated.

**TABLE IV**

**Effects of the formulation on serum-triglycerides and cholesterol levels**

| | Cholesterol (mmol/L) | | | Triglycerides (mmol/L) | | |
|---|---|---|---|---|---|---|
| | (weeks) | | | | | |
| Patient | 0 | 4 | 8 | 0 | 4 | 8 |
| 1 | 7.4 | 7.0 | 6.48 | 1.89 | 1.25 | 1.47 |
| 2 | 7.7 | 6.96 | 5.67 | 3.16 | 2.28 | 0.74 |
| 3 | 9.28 | 7.73 | – | 2.88 | 1.40 | – |
| 4 | 10.88 | 11.31 | 10.03 | 2.29 | 2.44 | 2.02 |
| 5 | 6.18 | 4.69 | 5.41 | 3.49 | 3.42 | 2.40 |
| 6 | 12.13 | 10.62 | 10.41 | 2.60 | 1.73 | 1.90 |
| 7 | 10.58 | – | 9.27 | 2.40 | – | 2.67 |
| 8 | 6.45 | 6.84 | 5.85 | 2.08 | 3.39 | 1.83 |
| 9 | 7.20 | 7.13 | – | 2.36 | 2.01 | – |
| 10 | 8.05 | 7.26 | 6.60 | 2.61 | 1.47 | 3.73 |
| 11 | 7.66 | 9.03 | 7.16 | 2.57 | 3.27 | 2.63 |
| 12 | 8.08 | 6.33 | 7.10 | 6.22 | 3.31 | 3.79 |
| 13 | 7.98 | 8.99 | 7.20 | 0.76 | 1.64 | 0.91 |
| 14 | 8.43 | 6.40 | 8.16 | 1.78 | 2.35 | 3.98 |
| 15 | 8.27 | 6.52 | 6.97 | 5.34 | 5.18 | – |
| 16 | 7.98 | 8.59 | 7.39 | 1.30 | 0.78 | 0.95 |
| $\bar{X}$ | 8.38 | 7.69 | 7.42 | 2.73 | 2.33 | 2.32 |

Table 4 shows that after 8 weeks there is a reduction of serum cholesterol and triglycerides in patients treated with this formulation. In the case of cholesterol, the reduction was statistically meaningful ($p < 0.05$ Wilcoxon), whereas no significant level was reached in triglycerides. Mean reduction in serum cholesterol levels was 12.2 %.

The analysis of the results revealed that treatment resulted in a significant decrease of cholesterol and low density lipoproteins. Treatment was 100 % effective since total cholesterol level in all patients was lower than at the beginning and the same applies for LDL when initial measurements were made. The percentage of LDL reduction was 13 %.

TABLE V

Effect of the formulation on low density lipoproteins (LDL) and very low density lipoproteins (VLDL) in plasma

| | Lipoproteins analyzed (mmol/L) | | | | | |
|---|---|---|---|---|---|---|
| | LDL | | | VLDL | | |
| Patient | 0 | 4 | 8 | 0 | 4 | 8 |
| | (weeks) | | | | | |
| 1 | 5.25 | 5.02 | 4.75 | 0.86 | 0.57 | 0.67 |
| 2 | 4.91 | 4.92 | - | 1.44 | 1.04 | 0.33 |
| 3 | 6.77 | 6.20 | - | 1.31 | 0.64 | - |
| 4 | 8.45 | 9.01 | 8.11 | 1.04 | 1.11 | 0.92 |
| 5 | 3.48 | - | 3.01 | 1.59 | 1.10 | 1.55 |
| 6 | 9.95 | 8.85 | 8.66 | 1.18 | 0.79 | 0.86 |
| 7 | 7.70 | - | 6.31 | 1.09 | - | 1.21 |
| 8 | 4.42 | 4.27 | - | 0.95 | 1.44 | 0.83 |
| 9 | 4.72 | 5.24 | - | 1.07 | 0.91 | - |
| 10 | 6.18 | 4.64 | 4.14 | 1.19 | 0.67 | 1.64 |
| 11 | 5.47 | 6.34 | 4.94 | 1.17 | 1.49 | 1.20 |
| 12 | 4.04 | 3.66 | 3.95 | 2.83 | 1.50 | 1.72 |
| 13 | 5.25 | 6.04 | 4.72 | 0.35 | 0.75 | 0.41 |
| 14 | 6.31 | 4.33 | 5.07 | 0.81 | 1.07 | 1.81 |
| 15 | 4.78 | 3.25 | - | 2.61 | 2.35 | - |
| 16 | 5.51 | 6.16 | 5.28 | 0.59 | 0.35 | - |
| $\bar{X}$ | 5.82 | 5.56 | 5.33 | 1.26 | 1.06 | 1.05 |

**Example 5**

A group of patients with hypercholesterolaemia were treated with 15 mg tablets of the formulation for 3 months. Results are shown in Table VI. In this example, there is also a cholesterol and triglycerides reduction in all treated patients.

Total cholesterol reduction amounted to 17.32 % and serum triglycerides to 16.3% after and before treatment.

**Example 6**

Doses of 0.5 and 5 mg of the alcohol mixture per kilogram of bodyweight were orally administrated to a group of New Zealand male rabbits during a month. The vehicle was administered to a control group included in the study. Blood samples were taken every 15 days to determine the parameters of lipidic metabolism. Results are shown in tables VII and VIII.

**TABLE VI**

**Effect of the formulation on cholesterol and serum triglycerides levels in a group of patients**

| | Cholesterol | | | | Triglycerides (mmol/L) | | | |
|---|---|---|---|---|---|---|---|---|
| Patient | 0 | 30 | 60 | 90 | 0 | 30 | 60 | 90 |
| | | | | (days) | | | | |
| 1 | 7.5 | 6.8 | 6.5 | 5.9 | 1.78 | 1.65 | 1.37 | 1.42 |
| 2 | 7.19 | 7.0 | 6.84 | 6.63 | 3.15 | 2.66 | 2.34 | 2.05 |
| 3 | 10.3 | 9.5 | 8.8 | 8.6 | 2.15 | 1.88 | 1.63 | 1.58 |
| 4 | 6.3 | 6.2 | 6.0 | 5.5 | 3.51 | 3.02 | 2.73 | 2.22 |
| 5 | 7.0 | 6.5 | 5.5 | 5.3 | 2.78 | 2.70 | 2.35 | 2.00 |
| 6 | 8.6 | 8.3 | 7.6 | 7.7 | 1.80 | 1.65 | 1.53 | 1.54 |
| 7 | 9.2 | 8.5 | 7.6 | 7.0 | 2.20 | 1.99 | 1.76 | 1.71 |
| 8 | 8.6 | 8.8 | 8.0 | 6.8 | 3.42 | 3.15 | 2.70 | 2.52 |
| 9 | 10.5 | 9.9 | 9.3 | 9.0 | 2.87 | 3.01 | 2.57 | 2.42 |
| 10 | 11.4 | 11.3 | 9.9 | 9.2 | 2.56 | 2.68 | 2.49 | 2.35 |
| $\overline{X}$ | 8.66 | 8.28 | 7.6 | 7.16 | 2.62 | 2.43 | 2.11 | 2.09 |

**TABLE VII**

**Effect of the formulation on cholesterol and triglycerides levels in rabbits**

| Animal | Dosage (mg/kg) | Cholesterol | | | Triglycerides (mmol/L) | | |
|---|---|---|---|---|---|---|---|
| | | 0 | 15 | 30 | 0 | 15 | 30 |
| | | | | | (days) | | |
| 1 | 0.0 | 3.25 | 2.60 | 4.40 | 1.23 | 1.09 | 2.12 |
| 2 | | 2.86 | 3.54 | 5.74 | 0.83 | 1.01 | 0.84 |
| 3 | | 1.54 | 2.72 | 3.24 | 1.73 | 1.40 | 1.43 |
| 4 | | 2.25 | 1.77 | 1.52 | 1.59 | 1.19 | 1.53 |
| 5 | | 1.90 | 2.94 | 2.47 | 0.96 | 1.34 | 1.01 |
| 6 | | 1.81 | 2.48 | 1.82 | 0.66 | 1.11 | 0.84 |
| 7 | | 2.00 | 3.09 | 2.26 | 2.11 | 3.29 | 1.27 |
| $\overline{X}$ | | 2.17 | 2.55 | 2.74 | 1.45 | 1.40 | 1.11 |
| 8 | 0.5 | 3.86 | 4.42 | 5.56 | 1.41 | 1.53 | 1.42 |
| 9 | | 1.96 | 2.69 | 2.00 | 1.26 | 1.01 | 0.59 |
| 10 | | 2.74 | 2.01 | 2.03 | 0.64 | 0.97 | 0.49 |
| 11 | | 2.38 | 2.61 | 2.47 | 1.32 | 1.42 | 0.48 |
| 12 | | 1.14 | 1.07 | 1.23 | 0.93 | 1.62 | 1.22 |
| 13 | | 1.38 | 2.13 | 2.54 | 1.03 | 1.01 | 0.71 |
| 14 | | 2.83 | 2.02 | 1.46 | 2.26 | 1.61 | 1.16 |
| $\overline{X}$ | | 2.32 | 2.42 | 2.47 | 1.26 | 1.31 | 0.86 |
| 15 | 5.0 | 1.48 | 1.67 | 1.76 | 0.93 | 0.98 | 0.69 |
| 16 | | 2.42 | 1.93 | 1.94 | 0.57 | 0.89 | 0.62 |
| 17 | | 1.86 | 1.89 | 1.83 | 0.79 | 1.30 | 0.69 |
| 18 | | 2.04 | 2.10 | 2.24 | 2.04 | 1.08 | 0.95 |
| 19 | | 1.96 | 1.67 | 1.53 | 0.88 | 0.68 | 0.63 |
| 20 | | 3.07 | 3.61 | 3.85 | 1.78 | 1.14 | 0.98 |
| 21 | | 5.53 | 3.02 | 2.04 | 3.28 | 1.38 | 0.64 |
| $\overline{X}$ | | 2.62 | 2.27 | 2.17 | 1.46 | 1.06 | 0.74 |

A significant difference was found in the content of serum cholesterol and triglycerides of rabbits treated with the formulation in a concentration of 5 mg of the mixture of aliphatic alcohols per kg of bodyweight by comparing its variation in time with that of the control group.

As can be observed in the Table, there is a significant reduction in VLDL with the dosage of 5.0 mg of the alcohol mixture per kg when compared to the control group after 30 days. Other parameters are not significantly affected, and e tendency is towards a reduced LDL, which is compatible with the results obtained for humans.

**TABLE VIII**

**Effect of the formulation on the lipoproteins in rabbit serum**

| Animal | Doses (mg/kg) | HDL 0 | HDL 15 | HDL 30 | LDL 0 | LDL 15 | LDL 30 | VLDL 0 | VLDL 15 | VLDL 30 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | (days) | | | | |
| 1 | 0 | 0.51 | 1.28 | 0.99 | 2.28 | 0.83 | 2.45 | 0.56 | 0.46 | 0.96 |
| 2 | | 1.17 | 1.49 | 1.33 | 1.31 | 1.60 | 4.03 | 0.38 | 0.45 | 0.38 |
| 3 | | 0.56 | 1.00 | 0.70 | 0.19 | 1.09 | 1.89 | 0.79 | 0.63 | 0.65 |
| 4 | | 0.65 | 0.77 | 0.62 | 0.51 | 0.46 | 0.21 | 1.09 | 0.54 | 0.69 |
| 5 | | 0.56 | 1.23 | 1.01 | 0.90 | 1.10 | 1.01 | 0.44 | 0.61 | 0.45 |
| 6 | | 0.94 | 1.32 | 0.95 | 0.57 | 0.66 | 0.49 | 0.30 | 0.50 | 0.38 |
| 7 | | 0.77 | 0.88 | 0.90 | 0.34 | 0.72 | 0.79 | 0.96 | 1.49 | 0.57 |
| $\bar{X}$ | | 0.74 | 1.09 | 0.89 | 0.83 | 0.78 | 1.30 | 0.70 | 0.63 | 0.51 |
| 8 | 0.5 | 0.81 | 1.07 | 0.82 | 2.41 | 2.66 | 4.10 | 0.64 | 0.69 | 0.64 |
| 9 | | 0.69 | 1.24 | 1.03 | 0.70 | 0.99 | 0.71 | 0.57 | 0.46 | 0.26 |
| 10 | | 1.25 | 1.02 | 0.79 | 1.18 | 0.55 | 1.02 | 0.31 | 0.44 | 0.22 |
| 11 | | 0.77 | 1.00 | 0.86 | 1.01 | 0.97 | 1.40 | 0.60 | 0.64 | 0.21 |
| 12 | | 0.56 | 0.43 | 0.49 | 0.16 | 0.10 | 0.19 | 0.42 | 0.73 | 0.35 |
| 13 | | 0.57 | 0.90 | 0.83 | 0.99 | 0.40 | 0.45 | 1.04 | 0.74 | 0.52 |
| 14 | | 0.82 | 0.88 | 0.49 | 0.33 | 0.77 | 1.39 | 0.48 | 0.46 | 0.32 |
| $\bar{X}$ | | 0.78 | 0.93 | 0.75 | 0.96 | 0.90 | 1.32 | 0.57 | 0.59 | 0.38 |
| 15 | 5.0 | 0.92 | 0.90 | 0.73 | 0.14 | 0.33 | 0.72 | 0.42 | 0.44 | 0.31 |
| 16 | | 0.83 | 1.11 | 0.73 | 1.33 | 0.42 | 1.39 | 0.26 | 0.40 | 0.28 |
| 17 | | 0.78 | 0.86 | 0.85 | 0.55 | 0.66 | 1.11 | 0.36 | 0.59 | 0.31 |
| 18 | | 0.56 | 0.95 | 0.70 | 0.72 | 0.44 | 0.67 | 0.93 | 0.49 | 0.43 |
| 19 | | 0.80 | 0.94 | 0.75 | 0.72 | 0.48 | 0.50 | 0.40 | 0.31 | 0.28 |
| 20 | | 0.56 | 1.32 | 1.19 | 2.41 | 1.77 | 2.22 | 0.81 | 0.52 | 0.44 |
| 21 | | 0.63 | 1.71 | 0.92 | 3.41 | 0.69 | 0.83 | 1.49 | 0.62 | 0.29 |
| $\bar{X}$ | | 0.72 | 1.11 | 0.84 | 1.33 | 0.67 | 1.06 | 0.66 | 0.48 | 0.33 |

**Example 7**

30 New Zealand rabbits having similar mean cholesterol values were distributed in three equal groups. One of them was taken as a control group, while the other two were given doses of 5 mg/kg of bodyweight of octacosanol and the alcohol mixture respectively. Blood samples were taken when treatment began, and 15 and 30 days later. Results are shown in Table IX. The study shows that 5 mg/kg of bodyweight treatment for a month tended to increase HDL while the HDL/LDL ratio decreased in relation to both the control group and the octacosanol group.

**TABLE IX**

**Effects of octacosanol and of the alcohol mixture on lipoproteins in rabbit serum**

| Serum levels of HDL-C | | | Serum levels of LDL-C (mmol/L) | | | HDL/LDL ratio | |
|---|---|---|---|---|---|---|---|
| 0 | 15 | 30 | 0 | 15 (days) | 30 | 0 | 30 |
| Octacosanol | | | | | | | |
| 0.59 ± 0.18 | 0.53 ± 0.18 | 0.95 ± 0.22 | 1.10 ± 0.52 | 0.88 ± 0,7 | 1.42 ± 0.32 | 0.61 ± 0.21 | 0.69 ± 0.23 |
| Alcohol mixture | | | | | | | |
| 0.52 ± 0.23 | 0.63 ± 0.24[t] | 1.05 ± 0.17[t] | 1.04 ± 0.33 | 0.91 ± 0.39 | 1.24 ± 0.45[t] | 0.62 ± 0.26 | 0.99 ± 0.44* |
| Control | | | | | | | |
| 0.54 ± 0.18 | 0.43 ± 0.12 | 0.93 ± 0.22 | 1.01 ± 0.5 | 0.91 ± 0.61 | 1.46 ± 0.44 | 0.55 ± 0.23 | 0.68 ± 0.17 |

[t]Is tendency and *$p < 0.05$ test t for non-paired series

**Example 8**

Daily administration of the formula resulting from this invention causes an increase of sexual activity in male rats which is expressed in a significant increase in the quantified number of erections and mounts during the observation of copulations with estrogenized females. These results are shown in Table X.

**TABLE X**

**Effect of oral administration of the formulation on the sexual behavior of male rats**

| Treatment (mg/kg) | Mounts | Erections | Animals mounting | Animals with erection |
|---|---|---|---|---|
| | ($\overline{X}$ ± DE) | | (%) | |
| Control | 8 ± 14 | 8 ± 13 | 50 | 66 |
| 0.5 | 21 ± 21* | 22 ± 21* | 75 | 75 |
| 5.0 | 24 ± 19** | 37 ± 44*** | 83* | 92* |
| 50 | 23 ± 11** | 23 ± 10*** | 100* | 100** |

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Note: Columns showing the number of mounts and erections were analyzed according to Mann Whitney U Tests and those showing percents were analyzed according to Fischer's Multiple Proportions Test

Experiments aimed at determining the effect of suspending the treatment for certain periods of time corroborate the above contention, since there is no significant difference as to sexual activity between formulation administered rats and controls. An increase in sexual activity has been observed in rats of up to 44 weeks of age when compared to controls.

**Example 9**

The effects of the mixture of primary fatty alcohols on the sexual behavior of male monkeys (**Macaca arctoides**) were studied after a daily dosage of the formulation (2.5 and 25 mg of active compound per kg of animal weight). The results are shown in Table XI.

TABLE XI

**Effects of oral administration of 2.5 and 25 mg/kg dosages on the sexual behavior of Macaca arctoides monkeys and the serum testosterone levels**

| Treatment (mg/kg) | Animal | Erections | Masturbations | Testosterone levels (nmol/L) |
|---|---|---|---|---|
| Control | 1 | 3 | 2 | 15 |
| | 2 | 2 | 2 | 13 |
| | 3 | 2 | 2 | 28 |
| | 4 | 0 | 0 | 26,3 |
| | 5 | 3 | 3 | 11,8 |
| | 6 | 0 | 0 | 21,4 |
| 2.5 | 1 | 21 | 20 | 22 |
| | 2 | 2 | 2 | 19 |
| | 3 | 3 | 2 | 22 |
| | 4 | 20 | 15 | 39 |
| 25 | 1 | 16 | 5 | 19,6 |
| | 2 | 7 | 5 | 14 |
| * | 3 | 3 | 2 | 21 |
| | 4 | 18 | 15 | 11,7 |

*$p < 0.05$ difference as compared to the control group according to Mann Whitney U Test

The results showed a significant increase in the number of penile erections and masturbations among treated animals when compared to controls. Evidently, there was no difference in the serum testosterone level between treated animals and controls, nor was there a correlation between these values and the number of erections and masturbations.

This experiment suggests that the administration of this formulation increases libido in treated animals, and that this effect is not related to the level of masculine hormones found in the group of monkeys.

Masculine sexual behavior in mammals includes libido, penile erection, ejaculation and orgasm. This behavior is determined by the release of testicular hormones acting on peripheral effector organs and provoking feedback effects in specific brain areas mainly located in the mediobasal hypothalamic region.

According to Buffum *et al* (1988), libido (or sex desire) is mainly controlled by the limbic system through the dopaminergic and serotonergic pathways. Minimal levels of testosterone are necessary to maintain libido but, according to what the author himself stated in 1982, additional increases of testosterone do not lead to a more intense urge. ogically enough, penile erection is affected as such by libido, but this is also a process regulated by the autonomic nervous system.

Consequently, the effects caused by the administration of a mixture of fatty alcohols may be a result of various mechanisms and are not directly deduced from the change in the hormone pattern. Yet, in an effort to determine how this mixture of primary fatty alcohols affects the sexual behavior of male rats, there were experiments which included the quantifying of copulations in castrated rats with and without mixture and in the presence of an exogenic supply of testosterone, as well as in castrated rats with and without that alcohol mixture, but in the absence of an exogenic administration of testosterone. The following example is taken from the latter series.

**Example 10**

Thirty castrated rats were taken and divided into three identical groups. One group was taken as a control and the other two were given 1 and 5 mg/kg of fatty alcohol The of the pharmaceutical formulation. The results of these experiments are shown in Table XII.

**TABLE XII**

**Effects of the mixture of primary fatty alcohols on the sexual behavior of castrated rats**

| Volumes of alcohol mixture | Before castration | | | After castration (under treatment) | |
|---|---|---|---|---|---|
| | Mount | Erection | $(\bar{X} \pm DS)$ | Mount | Erection |
| Control | 55 ± 46 | 55 ± 45 | | 17 ± 23+ | 15 ± 25+ |
| 1 | 56 ± 44 | 56 ± 44 | | 40 ± 50 | 40 ± 50 |
| 5 | 55 ± 45 | 55 ± 44 | | 55 ± 47 | 51 ± 47 |

*$p < 0.05$ with regards to control (Mann Whitney U Test)
+$p < 0.01$ with regards to previous observation (Wilcoxon)

This experiment showed that, in the absence of the main source and of an exogenic supply of testosterone, there are still very significant differences between rats which were administered the fatty alcohol mixture and the controls, which might be attributed in principle to an effect on the testosterone threshold value required in the central nervous system for maintaining libido.

## Claims

1. PHARMACEUTICAL FORMULATION CONTAINING A MIXTURE OF HIGHER PRIMARY ALIPHATIC ALCOHOLS obtained from sugar cane and consisting of a mixture of higher primary aliphatic alcohols ranging from 24 to 34 carbon atoms in a ratio of 0.5-5.0 % of the active compound, fillers, agglutinants, disintegrators, lubricants and other acceptable pharmaceutical excipients.

2. Mixture of higher primary aliphatic alcohols ranging from 24 to 34 carbon atoms obtained from sugar cane wax with the following composition:

| | |
|---|---|
| tetracosanol | 0.5 - 5.0 % |
| hexacosanol | 5.0 - 15.0 % |
| heptacosanol | 0.5 - 5.0 % |
| octacosanol | 50.0 - 80.0 % |
| nonacosanol | 0.5 - 3.0 % |
| triacontanol | 6.0 - 20.0 % |
| dotriacontanol | 1.0 - 10.0 % |
| tetratriacontanol | 0.0 - 2.5 % |

3. Use of a pharmaceutical formulation containing as an active component the mixture of higher primary aliphatic alcohols ranging from 24 to 34 carbon atoms obtained from sugar cane wax. The active compound is used as a hypocholesterolaemic in patients with high blood cholesterol levels.

4. Use of a pharmaceutical formulation containing as an active compound the mixture of higher primary aliphatic alcohols ranging from 24 to 34 carbon atoms obtained from sugar cane wax and used as a hypocholesterolaemic in patients suffering from hyperlypoproteinaemia type II. It causes a decrease in low density lipoproteins (LPL) in blood.

5. Use of a pharmaceutical formulation containing as an active compound the mixture of higher primary aliphatic alcohols ranging from 24 to 34 carbon atoms, obtained from sugar cane wax used as stimulant of sexual behavior.

6. Method used for the treatment of hypercholesterolaemia, hyperlyproproteinaemia type II and sexual behavior disorders, which includes a daily dosage 1-50 mg orally or parenterally.